Improving the Drug Delivery Efficacy of PVA Hydrogels

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CERTIFICATE

This is to certify that the dissertation entitled **"Improving the Drug Delivery Efficacy of PVA Hydrogels"** being submitted by Mr. Arnab Mahato and Ms. Itishree Ratha to the Department of Chemistry, National Institute of Technology, Rourkela, Orissa, for the award of the degree of Master of Science is a record of bonafide research carried out by them under my supervision and guidance. To the best of my knowledge, the matter embodied in the dissertation has not been submitted to any other University / Institute for the award of any Degree or Diploma.

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Arnab Mahato **Itishree Ratha**

CHAPTER 1

INTRODUCTION

1.1 Hydrogels:

Hydrogels are hydrophilic polymer networks that are able to swell and retain large amounts of water or biological fluids. Hydrogels work well in the body because they mimic the natural structure of the body's cellular makeup. As a result of this, the area of hydrogel research has expanded dramatically in the recent past, primarily because they perform well for biomedical applications [1]. Recent advances in the use of hydrogels have led to the potential to design artificial organs, deliver drugs to specific sites in the body in a controlled fashion and fabricate the extended wear contact lenses [2-6].

Hydrogels can imbibe water nearly 10-20 times its molecular weight and hence become swollen [7]. Their affinity to absorb water is attributed to the presence of hydrophilic groups such as –OH, –CONH–, –$CONH_2$–, and –SO_3H in polymers forming hydrogel structures [8]. Hydrogel technologies may be broadly applied to wound dressings [9], superabsorbent [10-12], barrier materials to regulate biological adhesions, biosensor and bioMEMs devices, tissue engineering and regenerative medicines, diagnostics and separation of biomolecules or cells [13, 14] and pharmaceuticals [15]. Hydrogels may be classified as natural or synthetic depending on the nature of their origin. They can be classified as neutral or ionic according to the nature of the side groups. On the basis of the physical structure of the networks, they can be classified as amorphous, semicrystalline, hydrogen-bonded structures or hydrocolloidal structures. Finally, they can be homopolymer or copolymer based on the method of preparation [1].

A truly amazing class of hydrogels that has found potential use for a wide variety of applications is the class of "smart" or "intelligent" hydrogels. The uniqueness of this class is due to the unusual volume changes that these polymers exhibit under the application of very specific stimuli. Smart hydrogels exhibit significant volume changes in response to stimuli such as changes in pH, temperature, electric field, ionic strength and light *etc.* Research efforts on the design of smart hydrogels for drug delivery application have increased significantly over the past few years; the idea behind this approach is that smart hydrogels will both expand and contract, forming a hydrogel "switch" that releases drug or protein in a controlled fashion. The developments in this area of research have been extensively reviewed periodically by various scientists [16-20].

Commonly studied ionic polymers for pH-responsive behaviour include poly(acrylamide) (PAAm), poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly(diethylaminoethyl methacrylate) (PDEAEMA) and poly(dimethylaminoethyl methacrylate) (PDMAEMA) [21].

Mostly studied thermosensitive polymers showing LCST in aqueous medium are Poly(*N*-isopropylacrylamide) (PNIPAAm,~32 ^{o}C), Poly(ethylene glycol) (PEG,~120 ^{o}C), Poly(methacrylic acid) (PMAA,~75 ^{o}C), Poly(vinyl alcohol) (PVA,~125 ^{o}C), Methylcellulose (MC, ~80 ^{o}C) and Poly(*N*-vinylcaprolactam) (PNVCPL, ~30 ^{o}C) *etc.*[22].

1.2 Benefits of Hydrogels in Biomedical Applications:

- Biocompatible and biodegradable.
- Can be injected or used as dressings.
- Good transport properties.
- Easy to modify into desired shapes such as slabs, moulds or films.
- Timed release of growth factors and other nutrients to ensure proper tissue growth.

- Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature or the concentration of metabolite and release their load as result of such a change.
- Natural hydrogel materials are being investigated for tissue engineering, which include agarose, methylcellulose, hylaronan, and other naturally derived polymers [23].

1.3 Applications of Hydrogels in Biomedical Field:

Hydrogels have been successfully used in biomedical fields due to their high water content and the consequent biocompatibility. Hydrogels are presently under intense investigation for drug delivery and controlled release of bioactive molecules. The water content in a hydrogel and cross linking density can determine the drug transfer in and out of the gel. Many new applications of hydrogels for biomedical are being proposed and constantly improvised. Honey hydrogels have been used for burn wound dressings. These hydrogels have matrix in which honey is cross-linked with chitosan. This system is readily acceptable in the body [24]. Hydrogel of gelatin and PVA (polyvinyl alcohol) along with blood coagulant have been formulated. The cell adhesive hydrogel ensured better effect than corresponding gel or ointment in controlling blood coagulation [25]. For aesthetic purpose, hydrogels have been implanted into breast to accentuate them. These hydrogels swell *in-vivo* in aqueous environment and retain water. These breast implants have silicone elastomer shell and are filled with polyacrylamide gel [26]. One of the major applications of hydrogels has been in the soft contact lenses. Many strategies have been developed to improvise the methods in ophthalmology. Soft contact lenses comprising vinyl-substituted polyphosphazene, 2-hydroxyethyl methacrylate, N-vinyl pyrrolidone and ethylene glycol dimethacrylate have been developed and reported for its high light transmittance and oxygen permeability [27]. Polysiloxane-Polyvinyl alcohol hydrogels have also been used for the production of soft

contact lenses [28]. Hydrogels also play a vital part in tissue engineering application. Many research works have been dedicated for the development of cartilage tissue engineering. Visible light cross-linkable hydrogel systems were synthesized using methacrylated glycol chitosan and three light blue initiators namely camphorquinone, fluorescein and riboflavin and were demonstrated in osteochondral and chondral defect models for potential cartilage tissue engineering [29].

1.4 PVA Hydrogels as Drug Delivery System:

Owing to its good film forming ability, long-term temperature and pH stability [30], PVA has proven itself as a better candidate in the class of biomaterials, hydrogels in particular. Moreover, PVA is bio-compatible, non-toxic and exhibits minimal cell adhesion and protein absorption as desired in biomedical applications [31]. Cross linked PVA membranes show good swelling property and are useful in sustaining drug release too [32]. Chemical cross linking generally results in modified and improved polymer properties such as mechanical, thermal and chemical stability. Mostly water-soluble polymers have been used as reagents that would undergo physical or chemical cross linking processes [33]. PVA hydrogels cross linked with maleic acid have been reported for colon targeted drug delivery [34]. Glutaraldehyde cross linked PVA hydrogel discs have also been reported for the release study of glipizide, an oral antidiabetic drug [35]. Even PVA cross linked glutaraldehyde hydrogels have been used for the controlled release of sulfosalicylic acid electrically [36]. PVA-chitosan blends have been used for the controlled use of nano-insulin [37]. Freeze/thaw cycling process is a method to obtain hydrogels without the use of any cross linker. PVA hydrogels prepared by freeze/thaw cycling are excellent biomaterial candidates as they exhibit a high degree of swelling in water, a rubbery elastic nature, are non-carcinogenic and can be readily accepted in the body [38]. For topical wound management, PVA-tetrahydroxyborate hydrogels have been synthesized and studied for potential drug delivery

system [39]. PVA and Chitosan hydrogels cross linked with tetraethoxysilane have been studied for the controlled release of aspirin [40]. Eco-synthesis is a method of synthesizing hydrogels without using any cross linking agents unlike the conventional method. PVA/Chitosan eco-synthesized blends have been reported for the release of the antibiotic sparfloxacin [41].

PVA based hydrogels have limited applications due to poor mechanical strength. Polymer blending is a simple yet attractive method to overcome this limiting factor and it provides improved physical and chemical properties to the hydrogels. Grafting and cross-linking are the two methods commonly employed to modify and improve the functional properties of the hydrogels. Commonly used cross linking agents for PVA based hydrogels include glutaraldehyde, maleic acid, tartaric acid or citric acid *etc*. Grafting of hydrogels usually involves the formation of semi- or full interpenetrating networks. An interpenetrating polymer network (IPN) is formed when a second hydrogel network is polymerized within a pre-polymerized hydrogel. This is typically done by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator. IPNs can be formed either in the presence of a cross-linker to produce a fully interpenetrating polymer network (full IPN) or in the absence of a cross-linking mechanism to generate a network of embedded linear polymers entrapped within the original hydrogel (semi-IPN).

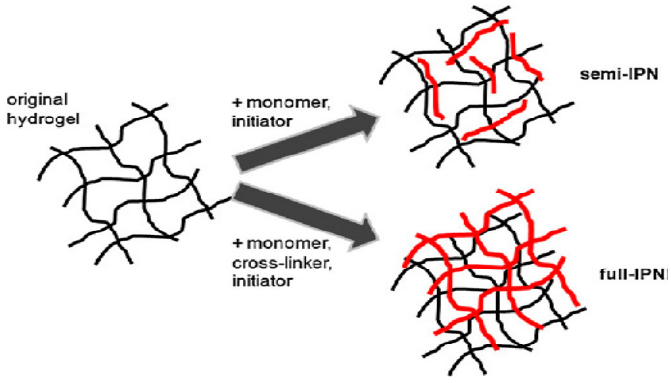


Fig. I Formation and structure of semi- and full interpenetrating polymer networks (IPNs).

Interpenetrating polymer network (IPN) microspheres of sodium CM-celluose and PVA have been prepared in w/o emulsion cross-linking method and studied for oral controlled release delivery of a NSAID, diclofenac sodium [42]. Semi-IPNs composed of PVA and poly(4-acetyl acryloyl Et acetate-co-acrylic acid) were synthesized via solution polymerization method and subsequently characterized [43]. Polyacrylamide grafted PVA/polyvinylpyrrolidone semi-IPN have been designed via a simple free radical polymerization route and the swelling properties was demonstrated [44]. A series of pH-sensitive semi-IPN composed of PVA and 21-arm star poly[2-(dimethylamino)ethyl methacrylate] was prepared and studied for the release of riboflavin [45]. Semi-IPN comprising chitosan grafted polyacrylic acid and polyvinyl alcohol were used as superabsorbent hydrogels and investigated for their water absorbency [46]. IPNs of sodium alginate and PVA prepared by solvent casting method have been developed for transdermal delivery of the anti-hypertensive drug prazosin hydrochloride [47]. PVA and PAA IPNs synthesized by non-conventional emulsion method without using any cross-linker and PVA-co-PAA/NaCl normal IPN hydrogel microspheres prepared by using glutaraldehyde-saturated toluene as cross linker have been compared for the release study of diltiazem hydrochloride [48]. Psyllium-PVA-acrylic acid hydrogels have been designed to study the release process of the antibiotic drug tetracycline hydrochloride [49]. Thermally cross-linked PVA and PAA hydrogels were studied for their swelling properties and the release property of the drug indomethacin [50].

1.5 Limitations of Hydrogels:

Classically, hydrogels can be used to deliver hydrophilic, small-molecule drugs which have high solubilities in both the hydrophilic hydrogel matrix and the aqueous solvent swelling the hydrogel. Although hydrogels are vastly used for biomedical applications, there are certain limiting factors associated with hydrogels:

- Low mechanical strength.
- Nonadherent.
- In contact lenses- lens deposition, hypoxia, dehydration and red eye reaction.
- Relatively inefficient in the case of
  a) Hydrophobic drugs which are sparingly soluble in both the aqueous and the hydrogel phases and
  b) Large macromolecular drugs (e.g. proteins, nucleic acids, *etc.*) which have diffusive limitations for partitioning into a hydrogel.

  Both of these classes of drugs are becoming increasingly important clinically.
- Sustained release of hydrophobic drugs into the aqueous environment.

1.6 Improving Drug Delivery Efficiency of Hydrogels:

The goal of drug delivery is to maintain the drug concentration in the body (plasma) within therapeutic limits for long periods of time. However, the high water content of most hydrogels results in relatively rapid release of drugs from the gel matrix, particularly in the case of hydrophilic drugs for which hydrogel delivery is typically applied. In this context, a range of strategies have been explored to reduce the release rate of drug from hydrogels either by enhancing the interactions between the drug and the hydrogel matrix and/or by increasing the diffusive barrier to drug release from the hydrogel.

- Both physical (charge interaction between polymer and the ionic drug) and chemical (by covalent linking of drug to polymer by using cleavable linkers) [51] means have been employed to enhance the interaction between a loaded drug and the hydrogel matrix to extend the duration of drug release.
- Another approach is to control the diffusion of drugs out of hydrogel matrices by modifying the microstructure of the hydrogel. For modifying the microstructure of hydrogels, interpenetrating polymer network (IPN) [52] and semi interpenetrating

polymer network (semi IPN) [53] have been used in preference to homopolymers with high concentration of cross-linking agent.

- A relatively improved method has been the incorporation of particulate systems (microspheres, liposomes, microemulsions, micelles, microgel *etc.*) into the hydrogel matrix to form composite or ‘‘plum pudding’’ hydrogel networks.

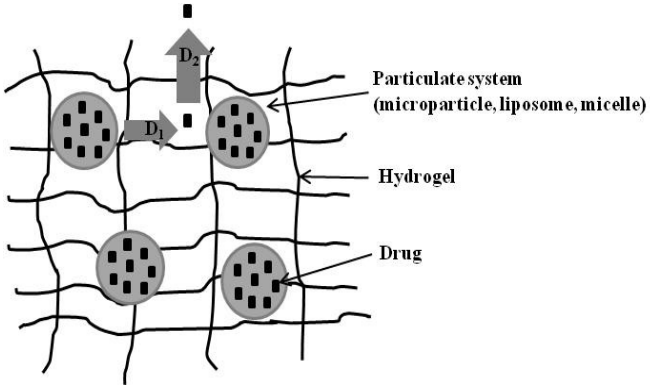


Fig. II ‘‘Plum pudding’’, composite hydrogels containing drug encapsulated in a particulate system. D_1 and D_2 represent the diffusion coefficients of drug out of the hydrogel (D_1: release from secondary release vehicle; D_2: diffusion through hydrogel).

1.7 Objective of the Study:

The inherent problem associated with hydrogel based drug delivery system is to achieve the sustained release of drug from the hydrogel matrix, which is often found to be diffusion controlled and difficult to have a control over. The aim of the present study is to improve the drug delivery efficacy of PVA hydrogels by using cyclodextrins as excipients.

CHAPTER 2

MATERIALS AND METHODS

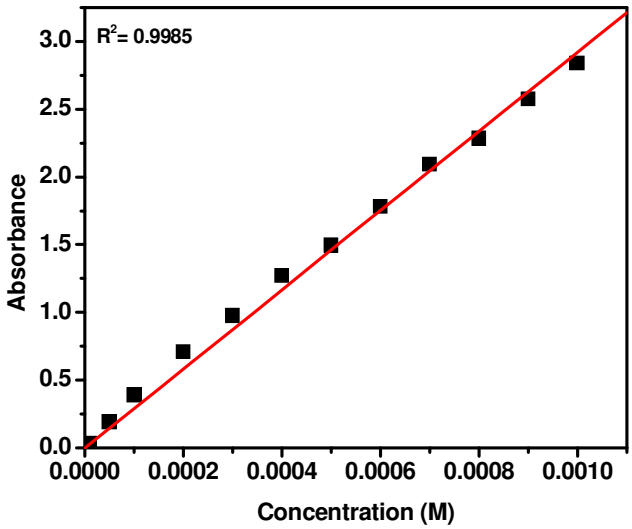
2.1 Materials:

PVA having molecular weight of 85,000 - 1, 24,000 and degree of hydrolysis 86.0-89.0% was purchased from S. D. Fine Chem., India. β-Cyclodextrin was procured from Sigma-Aldrich. Salicylic Acid of AR grade from Merck was utilized. Glutaraldehyde was obtained as a 25% (w/w) aqueous solution from Spectrochem Pvt. Ltd., Mumbai, India. Triply distilled water was used throughout.

2.2 Methods:

2.2.1 Calibration Curve of Salicylic Acid

In order to estimate the drug concentration during the drug release studies calibration curve for salicylic acid was constructed from the absorbance data. The plot of absorbance with the concentration of Salicylic Acid is shown below.



Calibration plot for Salicylic Acid in aqueous solution.

2.2.2 Film Preparation

10 wt% PVA was dissolved in water and heated at 80 °C for 4h. To the clear PVA solution, appropriate amounts of glutaraldehyde as cross linking agent and concentrated HCl as catalyst were added. The mixture was stirred briefly at room temperature to allow for the cross linking of glutaraldehyde onto the PVA solution. The mixing was effected at 200 rpm. The solution was then poured onto a clean and dried glass petri dish of known surface area to obtain a film. The film thus obtained was repeatedly washed with water to remove the unreacted monomers and the catalyst and dried *in-vacuo*. In a similar fashion, PVA films with adding β-Cyclodextrin were also synthesized. The quantity of glutaraldehyde was varied so as to get a series of cross linked hydrogels with varying concentrations of the cross linker. The various film compositions are shown in Table 1

Table 1. Compositions of hydrogels with varying amounts of glutaraldehyde

Sample number	Amount of PVA (wt %)	Glutaraldehyde (v/v)
1	10	0.01%
2	10	0.02%
3	10	0.05%
4	10	0.1%

2.3 Film Characterization

2.3.1 Equilibrium Swelling Ratio (ESR)

The swelling characteristic of all the prepared hydrogel films was studied. Hydrogel films (2x2 cm^2) were used for the determination of the swelling properties. The dried and pre-weighed hydrogel films were immersed in PBS (pH=7.4) solution at 37°C till equilibrium swelling was achieved. The samples were taken out at regular intervals and their weight was measured after gentle wiping in tissue paper to remove excess surface water. The degree of swelling was calculated as:

$$Degree\ of\ Swelling(\%) = \frac{W_w - W_d}{W_d} \times 100$$

Where W_w and W_d are the weights of the swollen and dried hydrogels, respectively.

2.3.2 X-Ray Diffraction

X-Ray diffraction studies were performed on a PANalytical X-Ray diffractometer. A CuK_α Radiation (λ=1.5405A°) was used at a scan rate of 2° at room temperature in the 2θ range 5°- 40°. Hydrogels in the form of dry films were used for the studies.

2.3.3 Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) experiment was performed by using DSC Q200 V24.4 Build 116 instrument. Dried samples of hydrogel films weighing 1–5 mg were taken in aluminum crucibles, sealed with Al-lid and then placed in DSC instrument. All the samples were first heated over the temperature range from 25 ^{0}C to 150 ^{0}C (first heating cycle); then cooled to 25 ^{0}C followed by heating up to 250 ^{0}C (second heating cycle), all at a heating rate of 10 ^{0}C min^{-1} under nitrogen. The reported results were taken from the second heating runs of the experiments in order to avoid experimental effects arising from the previous thermal history, structural relaxation and incomplete chemical reactions.

2.3.4 Scanning Electron Microscope

The analysis of the surface morphology of the hydrogel films was done using JOEL SEM, model JOEL- JSM 6480LV. The films were gold-coated under vacuum using JEOL-FRC 1200 SEM Gold Coater and then mounted on metal stubs using double-sided adhesive tapes.

2.4 *In-Vitro* Drug Release Studies

In vitro release of salicylic acid was carried out by placing the hydrogels loaded with the drug and sealed in dialysis membrane (Himedia) of MWCO = 12,000-14,000 in PBS (pH=7.4) at

37° C, mixing at 150 rpm. The drug release was determined by monitoring the absorbance at 296 nm for salicylic acid in a UV-Vis Spectrophotometer, Shimadzu UV-1800. The amount of drug released from the hydrogel films was estimated by comparing the absorbance with the calibration curve for salicylic acid.

CONCLUSION:

Hydrogels based drug delivery systems have gained momentum in the recent past considering their ability to imbibe large amounts of water or biological fluids and resemblance to living tissues in their elasticity. These unique properties render hydrogels useful materials for biomedical applications such as wound dressings, tissue engineering, soft contact lenses, protein sorption and recovery and artificial implants. Polyvinyl alcohol (PVA) is an excellent choice in the class of biomaterials because of its ease of hydrogel preparation, non-toxic and non-carcinogenic nature, relative cost-effective value and compatibility in the body. Despite these many promising factors, however, poor mechanical property has hampered the development of unmodified PVA as a stable hydrogel. Chemical cross-linking has, therefore, become a necessary tool to improve the structural integrity of PVA hydrogels. The present work focuses on the synthesis of glutaraldehyde cross-linked PVA hydrogels with and without the excipient cyclodextrin, followed by their subsequent characterization using ESR, XRD, DSC and SEM. A common anti-inflammatory drug, salicylic acid, has been chosen as the model drug. The synthesized PVA hydrogels were utilized as drug delivery system for salicylic acid.

REFERENCES

1. Jay Friedrich Künzler, *Hydrogels in Encyclopedia of Polymer Science and Technology*, Volumes 2, Part 1, 3rd Edition, February **2003** and references therein.
2. C. C. Lin, A. T. Metters, *Adv. Drug Deliv. Rev.* 58 (**2006**) 1379–1408.
3. P. Gupta, K. Vermani, S. Garg, *Drug Discov. Today* 7 (10) (**2002**) 569–579.
4. N. A. Peppas (Ed.), *Hydrogels in Medicine and Pharmacy*, vol. 1, CRC Press, Boca Raton, FL, **1986**.
5. M. Hamidi, A. Azadi, P. Rafiei, *Adv. Drug Deliv. Rev.* 60 (**2008**) 1638–1649 and references therein.
6. T. R. Hoare, D. S. Kohane, *Polymer* 49 (**2008**) 1993-2007.
7. S.W. Kim, Y. H. Bae, T. Okano, *Pharm. Res.* 9 (**1992**) 283-290.
8. N. A. Peppas, P. Buresa, W. Leobandunga, H. Ichikawa, *Eur. J. Pharm. Biopharm.* 50 (**2000**) 27-46.
9. A. K. Azad, N. Sermsinthan, S. Chandrkrachang, W. F. Stevens, *J. Biomat. Res. Part-B Appl. Biomat*. 69B (**2004**) 216-222.
10. F. Lionetto, A. Sannino, G. Mensitieri, A. Maffezzoli, *Macromol. Symp.* 200 (**2000**) 199-207.
11. E.V. Vashuk, E.V. Vorobieva, I.I. Basalyga, N.P. Krutko, *Mater. Res. Innov*. 4 (**2001**) 350-352.
12. M. J. Zohuriaan-Mehr, A. Pourjavadi, *J. Polym. Mat.* 20 (**2003**) 113-120.
13. A.C. Jen, M.C. Wake, A.G. Mikos, *Biotechnol. Bioeng*. 50 (**1996**) 357-364.
14. N. A. Peppas, Y. Huang, M-Lugo Torres, J. H. Ward, J. Zhang, *Annu. Rev. Biomed. Eng.* 2 (**2000**) 9-29.
15. A. Kumar, S. S. Lahiri, S. Punyani, H. Singh, *J. Appl. Polym. Sci.* 107 (**2008**) 863–871.
16. M. Patel, T. Shah, A. Amin, *Crit. Rev. Ther. Drug* 24 (**2007**) 147-202.
17. S. K. Roy, B. Prabhakar, *Trop. J. Pharm. Res.* 9 (**2010**) 91-104.
18. S. A. Pathan, Z. Iqbal, , J. K. Sahani, S. Talegaonkar, R. K. Khar, F. J. Ahmad , *Recent Pat. Drug Deliv. Formul.* 2 (**2008**) 177-188.
19. L. Klouda, A. G. Mikos, *Eur. J. Pharm. Biopharm.* 68 (**2008**) 34–45.
20. K. S. Soppimath, T. M. Aminabhavi, A. M. Dave, S. G. Kumbar, W. E. Rudzinski, *Drug Dev. Ind. Pharm.* 28 (**2002**) 957-974.
21. S. Zhao, M. Ca, Li-Yan Li, Wei-Lin Xu, *Iran. Polym. J.* 20 (**2011**) 329-340.

22. Y. Guan, Y. Zhang, *Soft Matter* 7 (**2011**) 6375-6384.
23. A. Singh, P.K. Sharma, V.K. Garg, G. Garg, *Int. J. of Pharm. Sci. Rev. Res*. 4 (**2010**) 97-105.
24. W. Tao, X. Zhu, X. Xue, D. Wu, *Carbohyd. Polym.* 88 (**2012**) 75-83.
25. D. Singh, C. Wahl, S. Heinhorst, S. E. Morgan, 239th ACS Meeting (**2010**).
26. K.N. Ben, D. Julie, T. Isabelle, D. Suzanne, P. Laurence, L. Lucie, *Eur. J. Radiol.* 78 (**2011**) 104-111.
27. A. Sung, T. Kim, G. Ye, Korean Republican Journal (**2010**).
28. A. S. Bobasheva, V. F. Danilichev, S. S. Ivanchev, E. V. Kaganova, V. N.; Ushakov, N. A. Pavlyuchenko, S. Ya. Khaikin, Russian Patent Application, (**2007**).
29. J. Hu, Y. Hou, H. Park, B. Choi, S. Hou, A. Chung, M. Lee, *Acta Biomateriallia* 8 (**2012**) 1730-1738.
30. S. M. Shaheen and K. Yamaura, *J. Controlled Release* 81(3) (**2002**) 367-377.
31. E. Bastuerk, M.V. Kahraman, *Polym. Compos.* 33 (5) (**2012**) 829-837.
32. S.G. Gholap, J.P. Jog, M.V. Badiger, *Polymer* 45(17) (**2004**) 5863-5873.
33. H. S. Mansur, R. L. Ore´fice, Alexandra A.P. Mansur, *Polymer* 45 (7) (**2004**) 193–202.
34. P. Basak, B. Adhikari, *J Mater. Sci: Mater Med* 20 (**2009**) S137-S146.
35. S.M. More, R.V. Kulkarni, B. Sa, N.V. Kayane, *J. Appl. Polym. Sci.* 116 (3) (**2010**) 1732-1738.
36. K. Juntanon, S. Niamlang, R. Rujiravanit, A. Sirivat, *Int. J. Pharm*. 356 (**2008**) 1–11.
37. Y. Zu, Y. Zhang, X. Zhao, C. Shan, S. Zu, K. Wang, Y. Li, Y. Ge *Int. J. Biol. Macromol.* 50 (1) (**2012**) 82-87.
38. C.M. Hassan, N.A. Peppas *Adv. Polym. Sci.* 153 (**2000**) 37–65.
39. J. D. Murphy, G. M. Sankalia, G. R. Loughlin, F. R. Donnelly, G.M. Jenkins, A.P. Carron, *Int. J. Pharm* 423(2) (**2012**) 326-334.
40. A. Islam, T. Yasin, I. Bano, M. Riaz, *J. Appl. Polym. Sci.* 124(5) (**2012**) 4184-4192.
41. A.M. Abdel-Mohsen, A.S. Aly, R. Hridna, A.S. Montaser, A. Hebeish, *J. Polym. Environ*. 19(4) (**2011**) 1005-1012.
42. S. Banerjee, L. Siddiqui, S.S. Bhattacharya, S. Kaity, A. Ghosh, P. Chattopadhyay, A. Pandey, L. Singh, *Int. J. Biol. Macromol*. 50 (**2012**) 198-206.
43. S. Lin, C. Yuan, A. Ke, Y. Li, N. Ouyang, Peop. Rep. China, (**2011**).
44. Q. Wei, Y. Luo, L. Gao, Q. Wang, D. Wang, *Polymer Sciences Series A*, 53 (**2011**) 707-714.

45. W. Wu, J. Liu, S. Chao, H. Tan, J. Li, F. Xu, X. Zhang, *Int. J. Pharm*., 416 (**2011**) 104-109.
46. J. Liu, W. Wang, A. Wang, *Polym. Adv. Technol*. 22 (**2011**) 627-634.
47. R. V. Kulkarni, V. Sreedhar, S. Mutalik, C. M. Setty, B. Sa, *Int. J. Biol. Macromol.* 47 (**2010**) 520-527.
48. D. Ray, P.S. Gils, G. Mohanta, R. Manavalan, P. K. Sahoo, *J. Appl. Polym. Sci* 116 (**2010**) 959-968.
49. B. Singh, V. Sharma, *Int. J. Pharm*. 389 (**2010**) 94-106.
50. H. Byun, B. Hong, S.Y. Nam, S.Y. Jung, J. W. Rhim, S.B. Lee, G.Y. Moon, *Macromol. Res*. 16 (**2008**) 189-193.
51. Y. X. Zhang, F. P. Wu, M. Z. Li, E. J. Wang, *Polymer* 46 (**2005**) 7695-7700.
52. I. Galeska, T. K. Kim, S. D. Patil, U. Bhardwaj, D. Chattopadhyay, F. Papadimitrakopoulos, *AAPS Journal* 7 (**2005**) 231-240.
53. I. Lynch, P. de Gregorio, K. A. Dawson, *J. Phy. Chem. B* 109 (**2005**) 6257-6261.
54. J. Xu, X. Li, *Acta Biomaterialia* 6 (**2010**) 486-493.
55. S. Ishiwata, M. Kamiya, *Chemosphere* 34 (**1997**) 783-789.